Cystic fibrosis

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Authors

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Abstract

Cystic fibrosis is an autosomal recessive disorder affecting the exocrine glands. It causes the secretions from these glands to become thick and viscous. There is a tendency to involve multiple organ systems. This article discusses the etiopathogenesis, clinical features and management of this problem.

Cystic fibrosis

Introduction:

Cystic fibrosis is an autosomal recessive disorder affecting the exocrine glands. It causes the secretions from these glands to become thick and viscous. There is a tendency to involve multiple organ systems. Commonly involved organ systems include: Nose, paranasal sinuses, gastrointestinal tract, skin and reproductive system. The incidence is rather high in caucasians. Figures reported from Unites States is about 1 per 2500 live births [1]. This high incidence has been attributed to improved diagnostic tools. Chronic rhinosinusitis and nasal polyposis are rather common in these patients. Studies reveal that the extent of sinus disease may have a bearing on pulmonary symptoms[2].

Pathophysiology of cystic fibrosis:

Cystic fibrosis is caused due to defects involving cystic fibrosis gene which codes for transmembrane conductance regulator protein (CFTR) which functions as chloride channel. This chloride channel is regulated by Cyclic AMP. Mutations involving cystic fibrosis transmembrane conductance regulator protein results in abnormalities involving chloride transport across epithelial cells / mucosal surfaces.

Six types of defects involving CFTR genes have been identified in cystic fibrosis [3].

Complete absence of CFTR protein synthesis

Defective maturation and early degradation of CFTR protein (the most common mutation)

Disordered regulation due to decreased ATP binding and hydrolysis

Defective chloride conductance

Diminished transcription due to promoter or splicing abnormality

Accelerated channel turnover from the cell surface

CFTR mutations have very poor penetrance. This indicates that genotype does not predict the severity of the disorder.

Defective CFTR causes decreased secretion of chloride and increased reabsorption of sodium and water across epithelial cells. This causes a reduction in the height of fluid lining the epithelium.

There is also associated dehydration of mucin causing it to thikcn. It also proves to be more stickier than normal mucous secretion. Bacteria gets adherent to this material causing smouldering infection. Secretions in the respiratory tract, Gastro intestinal tract and sweat glands are increased in viscosity making it difficult to clear.

Clinical manifestations of cystic fibrosis:

This is dependent on the organs involved. Probable disorders include:

Nasal polyposis

Sinusitis

Chronic diarrhoea

Rectal prolapse

Pancreatitis

Cholelithiasis

Cirrhosis of liver

Pathophysiology of sinusitis in patients with cystic fibrosis:

Exact mechanism is still not clear. Since chloride ions cannot be excreted sodium ions gets reabsorbed excessively. This increases the thickness and viscosity of the mucous blanket. Normal cilia present in the nose and paranasal sinuses find it difficult to push this viscid secretions out of the sinus / nasal cavities[4]. This causes accumulation of mucin within the sinus cavity. This accumulated mucin is an excellent culture medium for colonizing bacteria. This is one of the major reasons chronic sinus infections in these patients.

Other features predisposing to sinus infections in these patients include:

Ciliary dysfunction

Increased secretion of inflammatory mediators

Pseudomonas aeruginosa colonization

Pseudomonas colonization of nasal cavity is commonly reported in patients with cystic fibrosis associated with nasal polypi, where as it is not so common in patients with cystic fibrosis without nasal polyposis[5]. Pseudomonas organisms produce toxins which has deleterious effects on the normal ciliary beat. These toxins include: Hemolyzin and Pyocyanin. Out of these two toxins Pyocyanin slows down the ciliary beat appreciably causing mucin stasis within nose and paranasal sinuses. Pyocyanin has been suspected to play some role in the development of nasal polyposis in these patients[6].

Role of allergy in the pathophysiology of nasal polyposis in patients with cystic fibrosis:

Role of allergy in the pathophysiology of nasal polyposis in patients with cystic fibrosis is still not clear. Statistical prevalance of atopy in patients with cystic fibrosis does not differ significantly between those with nasal polyposis and those without nasal polypi[7]. However current studies reveal that patients with cystic fibrosis who manifest with positive skin prick test have been found to be commonly colonized by pseudomonas. As stated previously pseudomonas colonization has a role to play in the pathophysiology of development of nasal polypi in these patients. Hence it has been widely postulated whether it is the allergic reaction perse or allergic reaction to fungi could be the cause for nasal

polyposis in these patients. Allergic reaction to aspergillus fumigatus has been documented in patients with bronchopulmonary aspergillosis in patients with cystic fibrosis [8].

Pathological differences between nasal polypi in patients with cystic fibrosis and in those without cystic fibrosis:

Histopathological characteristics differ between nasal polypi found in cystic fibrosis from those of non cystic fibrosis patients.

The table given below provides just a glimpse into the histopathological differences between these two entities.

Nasal polypi in cystic fibrosis	Nasal polypi in non cystic fibrosis patients
Neutrophilic infiltration	Eosinophilic infiltration
Basement membrane of polyp thin and delicate	Thick basement membrane
Submucosal hyalinization absent	Submucosal hyalinization present
Mucous glands contain acid mucin	Mucous glands contain neutral mucin
Nasal polypi common in children with cystic fibrosis	Nasal polypi are rather rare in children without cystic fibrosis

It has been suggested that all children with nasal polyposis should undergo sweat test to rule out cystic fibrosis. Sweat chloride level of more than 60 mEq/L is considered to be diagnostic of cystic fibrosis. This should eventually be followed up by genetic testing and proper councelling.

Role of imaging in diagnosis / evaluation of patients with cystic fibrosis:

Routine x-rays are of no value in these patients. CT scan of nose and paranasal sinuses is the preferred radiological investigation of choice in these patients.

CT scan findings include:

Frontal sinus hypoplasia

Maxillary sinus expansion with medialization

Loss of medial maxillary wall

Mucocele formation in maxillary sinuses

Frontal sinus hypoplasia has been attributed due to diminished post natal growth of these sinuses due to the presence of chronic inflammation.

Management:

Medical:

This should be considered to be the first step in a series of steps.

Saline irrigation:

Regular saline irrigation of nasal cavities clears the nasal secretions, and also gets rid of inflammatory mediators from the nasal mucous membrane. Crusts become soft on exposure to saline and can hence be easily removed after the wash. Children who underwent regular saline wash of their nasal cavities on a regular basis rarely needed surgery for nasal polyposis.

Topical baby shampoo lavage has found favour recently. It helps in removing / dislodging biofilms from inside the nasal cavity [9].

Role of steroids:

Use of topical steroids[10] have been found to play an important role in reducing the size of nasal polypi in these patients. It has been demonstrated in children who are on systemic steroids for their lung condition showed a significant reduction in the size of nasal polypi.

Role of antibiotics:

Since psudeomonas infections play an important role in the development of nasal polypi in patients with cystic fibrosis, antibiotic therapy directed against pseudomonas organism plays an important role. Topical Tobramycin can be used as nasal wash in these patients. This not only reduced the pseudomonas nasal load but also caused a significant reduction in the size of nasal polypi. This was reported widely by Moss et al [11].

Role of Dornase alpha [12]:

In patients with cystic fibrosis, a large amount of DNA released from degenerating neutrophils have been implicated as the cause of increased viscosity of nasal secretions. Dornase alpha a recombinant human deoxyribonuclease when administered in these patients has reduced the viscosity of bronchial and nasal secretions. Intranasal administration of this drug has had beneficial effects in these patients.

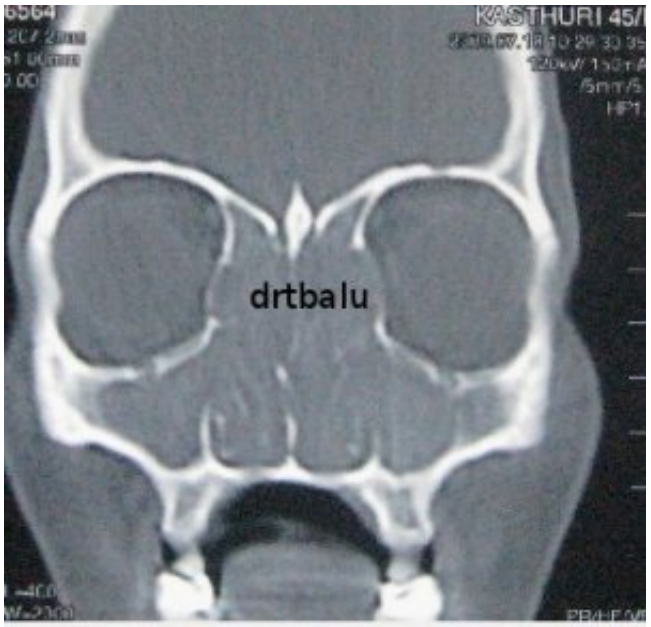
Role of Ibuprofen:

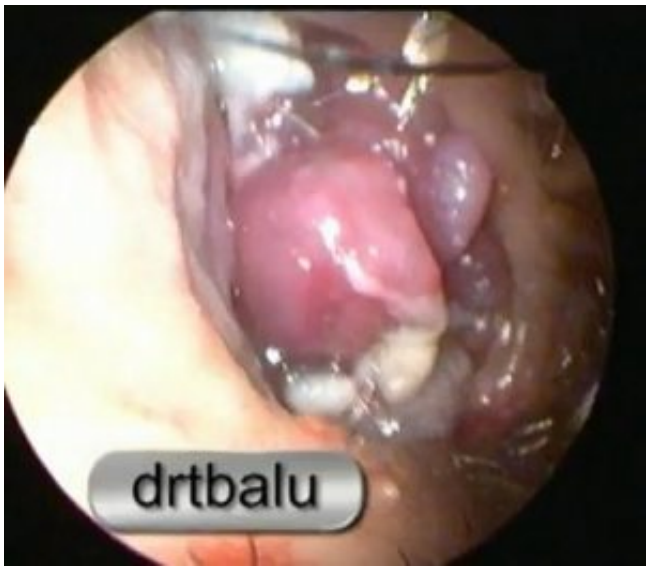
Upregulation of cyclooxygenase (COX) enzymes has been identified in nasal polypi of patients with cystic fibrosis. High dose ibuprofen which blocks these enzymes has shown promise in these patients. High dose ibuprofen has reduced the size of nasal polypi in these patients [13].

Surgery:

Role of surgery in these patients is only when conservative medical management fails. Major risk involved in surgery is due to bleeding. Since these patients have vitamin K malabsorption, coagulation disorders are common. After surgery nasal block is dramatically reduced. Endoscopic sinus surgical procedures have replaced the conventional polypectomy. Recurrence is common in these patients even after successful removal. Recurrence is common in about 60% of treated patients. In patients with maxillary sinus mucoceles a wide middle meatal antrostomy will facilitate its drainage.

Coronal CT scan of nose and paranasal sinuses in a patient with cystic fibrosis





Picture showing nasal polyposis with infected secretions in a patient with cystic fibrosis

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